REMARKS

Status of the Claims

Claims 1, 2, 8-12, and 41-52 are now pending in the present application, Claims 3-7 and 13-40 having been cancelled in response to an earlier restriction requirement. In addition, applicants have amended Claims 1 and 8 to more clearly define the present invention, Claim 2 has been amended to correct a minor typographical error, and new Claims 49-52 have been added.

Claim of Priority

The Examiner has noted that a foreign application (0019744.2, England) has been made of record in the file. Applicants have no knowledge of how that application came to be of record. Applicants did not submit that reference with a claim of priority, and after examining the reference provided by the Examiner, applicants do not recognize the reference. It appears that the foreign application has somehow through error been inadvertently incorporated into the record of the application and may have been intended for a different application. However, applicants have made a claim to priority in two U.S. provisional patent applications, as referenced in the specification of the present application as filed. The two provisional applications for which a claim of priority under 35 U.S.C. § 119(e) has been made are Serial No. 60/240,125, filed on October 12, 2000, and Serial No. 60/242,734, filed on October 23, 2000. The priority claim to these two provisional applications is also correctly listed on the Filing Receipt issued by the United States Patent and Trademark Office.

Claims Rejected under 35 U.S.C. § 102 in View of Wang

The Examiner has rejected Claims 1, 2, and 41-44 as being anticipated by U.S. Patent No. 5,922,617 (Wang et al.). Wang discloses a method and apparatus for determining interactions between different components of the same or different type of composition. The apparatus includes arrays of samples in tracks, where light emitting labels are excited and emitted light detected. Various modifications are discussed for the invention of Wang, such as using pre-prepared segments that may then be attached to a disk for assaying. The Examiner concludes that Wang teaches an equivalent to applicants' claimed invention. Specifically, the Examiner notes that Wang discloses optical reporters, and carriers that can be distinguished based on size, shape, color, and intensity.

Applicants respectfully disagree with the Examiner's rejection, particularly in view of the amendment to the claims set forth above, for the following reasons. The rejection based on Wang requires a modification of Wang that is neither taught nor suggested in the cited art, and even when

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the cited art is modified as proposed by the Examiner, the result is not equivalent to applicants' invention as defined in independent Claim 1 as amended.

The Examiner has acknowledged applicants' argument that Wang does not teach adding carriers to vessels first, then adding reporters to the vessel, such that the attachment occurs in the vessel. However, the Examiner has indicated that this distinction is "in the purview of the cited art" because the different sequence of steps achieves the same result – a library of reporter labeled carriers. The Examiner further notes that the changes required of Wang's method to achieve the present claimed method of applicants are merely a matter of a choice of experimental design. Applicants respectfully disagree with this conclusion, because there is no suggestion in the cited art about the desirability of modifying Wang's method in the manner required to achieve applicants' claimed invention. It is also important to note that simply because two different methods achieve a similar result does not mean one of the methods is not patentably distinguishable over the other. Two methods are not patentably distinguishable if the modifications required to achieve identical steps would have been obvious to one of ordinary skill in the art. Yet, in this case, the cited art does not provide any evidence or suggestion that such modifications would have been obvious. Further, the Examiner has rejected Claim 1 as being *anticipated* by Wang, yet the rejection requires a *modification* of the steps taught by Wang's disclosure, and it appears the rejection ought to be based on obviousness rather than anticipation. But regardless, there is no evidence of any teaching or suggestion in the cited art that would lead one of ordinary skill to modify Wang's disclosure to achieve the present claimed invention of applicants.

The Examiner has stated that Wang's disclosed method and applicants' method achieve the same result, i.e., a complex for detection including a bead and a reporter. That assertion fails to recognize that applicants' steps achieve a complex including a carrier and a reporter, to which no additional compound of interest has been added, whereas Wang achieves a complex including a bead, an optically distinct reporter *and* a first compound to be exposed to a second compound. The libraries of the cited art and the present claimed invention are not equivalent, for the reasons further explained below.

Claim 1 now recites that when initially added to the vessels, none of the plurality of carriers has compounds of interest or reporters yet bound to them, and that the library constructed is blank, since no compounds of interest have yet been added to the optically distinct reporter labeled carriers.

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This concept is clearly described in applicants' specification (see page 12, last paragraph). Blank libraries of this sort are very useful, because they can be mass produced. Also, a portion of the library can be used for DNA analysis, while another portion is used for drug discovery assaying. The blank library is generated by attaching optically distinct reporters to the carriers. Subsequently, to use the library, compounds of interest can be attached to the already labeled carriers. It should be noted that the terms "blank" and "compound of interest," while being newly introduced into the claims, do not represent new matter because the concepts are clearly described in applicants' specification. Specifically, the specification explains that "a significant advantage of the present invention is that since no chemical compounds are attached to the beads during the encoding process, a large manufacturing run of a single set of uniquely encoded beads can be used for any number of different compounds, which are subsequently synthesized on or attached to the beads (page 12, lines 30-34)."

It is important to note that for the blank library to be functional, after the reporters have been attached to the carrier, there must be sufficient room left on the carrier for compounds of interest to be attached. Applicants' specification teaches that the use of optically distinct reporters enables an increase in the availability of the carrier surface for chemical synthesis (i.e., the attachment of compounds of interest to be analyzed; see page 9, lines 15-19, and elsewhere in the specification). In contrast, Wang teaches, in reference to FIGURES 1A and 1B, that each bead is "substantially completely covered with the bound component" (see column 13, lines 19-20 of the reference). Thus Wang discloses that there is no room for an additional compound to bind to the carrier. Thus, the present invention is characterized by a blank library of carriers, each carrier being labeled by an optically distinct reporter and configured such that a compound of interest can still be attached to each carrier in the library.

Both applicants' library and Wang's array can be used to screen large numbers of compounds, by exposing a first compound bound to the carrier to a second compound. Significantly, Wang teaches an array/library that *already includes* first compounds (not just optically distinct reporters) bound to the carrier. Clearly, changing the sequence of steps (i.e., when reporters are attached and when compounds to be analyzed are attached) makes it clear that Wang's library is different than applicants' claimed library. Also, Wang does not teach that the step of labeling a carrier with an optically distinct reporter and the step of attaching a compound of interest be separated into two distinct steps.

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While the Examiner is correct that Wang discloses fluorescent dyes can be used in conjunction with carriers, it is important to note that Wang does not teach attaching the dyes to the carrier separately from attaching compounds of interest. Rather, Wang teaches that the dye attached is incorporated into a compound that will be analyzed (i.e., a fusion protein), such that substantially the entire surface of the carrier is filled with fusion proteins including the fluorescent dye. The optical reporter is actually incorporated into the compound of interest, and that complex is attached to the carrier in Wang. Because the optical reporter is part of the compound to be analyzed, and because Wang specifically teaches that the surface of the carrier be filled, once the reporter is incorporated into the carrier via the fusion protein, no other compounds can be added.

Fluorescent dyes and fusion proteins are disclosed by Wang at column 5, lines 7-29. As described throughout Wang's disclosure, various compounds such as nucleic acids, DNA sequences, RNA sequences, and proteins can be coupled with beads and placed into an array to enable analysis of the compound, in response to exposure to other compounds. Clearly, coupling fusion proteins that include fluorescent dyes to a carrier, as described by Wang, results in a carrier, a reporter and a compound to be analyzed, whereas applicants library includes labeled carrier to which no compound of interest has been added.

It is very important to understand that the function of applicants' optical reporters is to enable carriers from specific vessels to be distinguishable from carriers in other vessels. When compounds to be analyzed are added to carriers from specific vessels, and a record is made of what compound has been added to what vessel, identifying the carrier enables the compound to be identified. Wang notes that identifying specific carriers might be desirable and specifically teaches that a binary code be used for identifying the carrier (see column 7, lines 10-19). While the Examiner is aware of this teaching by Wang, it is unclear why the Examiner asserts that Wang does not "explicitly refer" to such a binary code for identifying individual particles. Wang clearly teaches that the binary code disclosed in U.S. Patent No 5,565,324 be used to encode individual particles (i.e., beads or carriers). It appears that the Examiner believes that disclosure about the use of dots and fluorescent dyes relates to labeling carriers (column 9, lines 3-24), and that such disclose provides an alternate mechanism for labeling carriers. The paragraph to which the Examiner cites is reproduced below in its entirety:

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> In addition, by using headers one can code for an address. Thus, by using pits or bars having different sizes and/or different spacing, one can create coding which will define the track, segment or other feature associated with one or more bound components. By knowing what was introduced onto the solid substrate in conjunction with the header, one can read what is present at a particular site on the solid substrate. The headers can be placed in conjunction with the various structural elements of the solid substrate or pre-prepared arrays, so that one can readily determine what the bound component or the labile component is, which is in juxtaposition to the header. The coding can be introduced in any of the conventional ways, such as photolithography and etching, laser burning, chemical erosion, printing or stamping, etc. *Alternatively, one may use dots or stripes of fluorescent dyes, the same or different dyes, so as to create an address where one can define the site by the order of emission wavelengths, intensity, size, or the like.* In some instances the coding may not be specific for a single entity, it being sufficient to know the identity of a relatively small group, usually under 500 entities, more usually under about 100 entities. By repetitive iteration, one may then determine the specific entity (Wang, column 9, lines 3-24; emphasis added).

The disclosure about dots and fluorescent dyes in Wang does not relate to encoding or identifying carriers. The dots and fluorescent dyes described above are not attached to the carriers. That portion of the reference has been taken out of context. The intervening text between the description of using binary coding to encode the carriers (column 7, lines 10-20) and the alternative use of dots and dyes (column 9, line 17-20) cannot be ignored. When the entire paragraph is read, it is clear that the dots and dyes referred to in column 9 are an alternative to laser burning, chemical erosion, printing, and stamping techniques that are used to *mark the substrate* in which the wells/grooves/pits are formed. Wang refers to this as a *header* that codes an address on the substrate. Basically, a subsection of the substrate (which Wang teaches is preferably a disk) is labeled using dots or dyes, so that the carriers inserted into wells or grooves (i.e., vessels) in that portion of the substrate can be identified. However, the identifying indicia ***are not attached to the carriers***. Instead, the identifying indicia are ***part of the vessel into which the carriers are placed***. If someone mistakenly mislabels the vessel, the carriers in that vessel will not be accurately identified. Applicants' reporters are attached to the carriers and enable the carriers to be identified. It is very important to recognize that Wang discloses: fluorescent dyes combined with fusion proteins attached to the carrier such that *no additional room* is available for other compounds to attach to the carrier, binary labeled carriers, and vessels labeled with dots and fluorescent dyes.

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The library disclosed by Wang is therefore not identical to the library achieved using the method defined in applicants' Claim 1, and there does not appear to be any teaching or suggestion in the cited art for modifying Wang to achieve an identical library to that produced by applicants' claimed method. Wang does not teach a library of carriers having reporters attached to the carriers but no compounds of interest. Because dependent claims are patentable for at least the same reasons as the claims from which they depend, Claims 2 and 41-44 are patentable for the same reasons as Claim 1. Accordingly, the rejection of Claims 1, 2, and 41-44 as being anticipated by Wang should be withdrawn.

Referring now to the rejection of Claims 43 and 44, in these claims, applicants recite that the carriers can be distinguished based on color and intensity of color. The Examiner appears to assert that the *headers* disclosed by Wang (column 9, lines 17-20) enable the *carriers* to be distinguished in the cited art. But, as discussed above, the headers (characterized by dyes and dots of different color, size, intensity, etc.) of Wang are formed on the substrate into which the vessels are formed, not on the carriers themselves. Wang's disclosed approach is not equivalent to applicants' claimed method, in which carriers can be can be distinguished by color and intensity of color. If four bottles of water having different salt content were each labeled with a different color, the *bottles* can be distinguished. Yet the water in the volumes having different salt content appear identical, and once removed from their distinguishable vessels, the volumes of water are not visually distinguishable. If Wang's carriers are removed from the labeled portions of the disk, the carriers themselves are not optically distinct based on color or intensity of color, because that information is conveyed by the header, not by the carriers themselves. The Examiner correctly points out that Wang discloses carriers having distinguishable sizes and shapes, but Wang does not disclose the elements of color and intensity being associated with the carrier, only the header. For this additional reason, the rejection of Claims 43 and 44 as being anticipated by Wang should be withdrawn.

In referring to applicants' previously presented argument that Wang does not teach that ***each*** vessel must include a different set of optically labeled carriers, the Examiner cites to a portion of Wang (column 7, line 60 to column 8, line 10) that discusses a use for Wang's bead library. However, that section does not state that *each* different vessel has a set of optically labeled carriers distinguishable from the set of optically labeled carriers in each other vessel. Wang notes that each vessel can include carriers that have the same compound attached to them, or different compounds,

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but Wang never states that the different compounds *must be* different optical reporters. Wang discloses many compounds that can be attached to a carrier that are not optical reporters. In responding to this argument, the Examiner also refers to column 9, lines 17-20, which as noted above, has been taken out of context.

Claims Rejected under 35 U.S.C. § 103 over Wang in view of Furka

The Examiner has also rejected Claims 8-12 and 45-48 under 35 U.S.C. § 103(a) as being obvious over Wang in view of Furka (WO 93/24517). It appears that the Examiner admits that Wang does not disclose carriers that are optically distinct; however, the Examiner has rejected Claims 41-44 as being anticipated by Wang, based on an assertion that Wang discloses optically distinct carriers. Thus, the reasoning employed in the obviousness rejection does not appear to be consistent with the reasoning employed in the anticipation rejection.

Regardless, applicants have amended independent Claim 8 in the same manner as independent Claim 1. The blank library produced based on the method in Claim 8 does not yet include compounds of interest attached to the carriers. Instead, it only includes reporters. The blank library can be used to analyze any number of different types of compounds, such as DNA fragments or drug assays, based on the types of compounds attached to the pre-labeled beads. The Examiner noted, "...both Wang et al. and Furka disclose a method of preparing a library of beads with bound components such as peptide...." But, such libraries already have the components to be analyzed coupled to them. A library in accord with applicants' claimed invention includes only labeled carriers, and is distinguishable over Wang for the reasons already noted above. Nothing in the disclosure of Furka would lead one of ordinary skill in this art to a method for preparing a library of labeled carriers with no compounds of interest yet attached. Therefore, Claim 8 is patentable. Because dependent claims are patentable for at least the same reasons as the claims from which they depend, Claims 9-12 and 45-48 are patentable for the same reasons as Claim 8. Accordingly, the rejection of Claims 8-12 and 45-48 as being obvious over Wang in view of Furka should be withdrawn.

Referring now to the rejection of Claims 11 and 48, applicants recite that the carriers themselves can be distinguished based on an intensity of color. The Examiner appears to assert that the ***headers*** disclosed by Wang (column 9, lines 17-20) enable the *carriers* to be distinguished based on an intensity of color. As discussed above, the headers (characterized by dyes and dots of different

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color, size, intensity, etc.) are formed ***on the substrate*** into which the vessels are formed, not on the carriers themselves. Neither Furka nor Wang discloses carriers that can be distinguished based on an intensity of color, and no combination of the cited art could thus achieve an equivalent invention. For this additional reason, the rejection of Claims 11 and 48 as being obvious over Wang in view of Furka should be withdrawn.

Claims Rejected under 35 U.S.C. § 102 in View of Still

The Examiner has also rejected Claims 1, 2, 8-12, 43-44, and 47-48 under 35 U.S.C. § 102(b) as being anticipated by Still (U.S. Patent No. 5,565,324). The Examiner notes that Still discloses combinatorial chemistry methods in which identifiers are added at each stage of a synthesis, and that Still teaches both a split/add/pool method as well as a method wherein the particles are not pooled between stages. Applicants respectfully disagree with the Examiner's assertions and conclusions for the following reasons.

The present invention is distinguishable from the methods disclosed by Still because Still teaches that identifiers are added to a particle during each stage of a synthesis of a compound bound to the particle. The Examiner cites to a portion of Still that specifically states "One would then add appropriate agents to each of the individual containers to process them in stages and add the identifiers that encode the reagent and stage" (column 15, lines 21-23). Clearly, in Still, the identifiers are not being added to the particle ***before*** the compound of interest is added to the particle, as recited in applicants' amended claims, but concurrently with the identifiers. Still's method achieves a library of particles including compounds of interest. As discussed above, applicants' library is blank, since the carriers are labeled with optically distinct reporters, but the compounds of interest have not yet been added.

The library disclosed by Still is not identical to the library achieved using the method defined in applicants' independent Claims 1 and 8, and there does not appear to be any suggestion in the cited art for modifying Still to achieve an identical library. Claims 1 and 8 are therefore patentable over the cited art. Because dependent claims are patentable for at least the same reasons as the claims from which they depend, Claims 2, 9-12, 43-44, and 47-48 are patentable for the same reasons as Claims 1 and 8. Accordingly, the rejection of Claims 1, 2, 8-12, 43-44, and 47-48 as being anticipated by Still should be withdrawn.

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Another distinguishing element is that Still does not teach or suggest that the carriers themselves are optically distinct. Still teaches that a wide variety of carriers can be used, but it does not appear that Still teaches or suggests using a mixture of carriers that are optically distinct to generate a library that includes carriers, which themselves are optically distinct. Still discusses carriers at column 10, lines 5-51. Significantly, Still does not provide any disclosure that teaches or suggests that mixtures of optically distinct carriers be used in a combinatorial synthesis. Claims 2, 8-12, 43-44, and 47-48 each recite optically distinct carriers. With respect to Claims 43-44 and Claims 47-48, it appears that the Examiner concludes that the fluorescent or chemiluminescent tags disclosed by Still read on the distinguishing by color and intensity as recited in these claims. It must be noted that Claims 43-44 and Claims 47-48 recite that the color and the intensity *of the carriers themselves* enable carriers to be distinguished from different carriers. Still teaches that the color of the tags, not the color of the carriers, is used to distinguish different carriers. For this additional reason, the rejection of Claims 43-44 and Claims 47-48 as being anticipated by Still should be withdrawn.

Patentability of New Claims

Claims 49-52 have been added and are fully supported by the specification.

Claim 49 is based on Claim 1, and recites that each member of the library includes a carrier to which at least one optically distinct reporter is attached, but a compound of interest is not included. Each of the references cited discloses complexes that include a carrier, a reporter, and ***at least one compound of interest***. Claim 49 is therefore patentable over the cited art.

Claim 50 is based on a combination of Claim 1 with the technique described in applicants' specification relating to applicants' FIGURE 14, regarding a method of using a plurality of different optical reporters to achieve a library of reporters expressing all possible binary codes. It should be understood that Claim 50 is not simply a method of producing optically distinct reporters, but a method for producing a library of optically distinct, reporter labeled carriers. Thus, while the Examiner has restricted claims based on FIGURE 14, the claims previously restricted were based on making reporters, not making a library of optically distinct, reporter labeled carriers, by using reporters prepared in a specific fashion. In Claim 50, the size of the library is a function of the number of possible binary codes that can be produced using a given set of different optically distinct reporters. Reporters are added to reaction vessels such that each reaction vessel receives the reporters

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required to achieve the binary code corresponding to that reaction vessel. Carriers are then added to each reaction vessel, and the reporters in each reaction vessel are attached to the carriers to achieve a library of optically distinct reporter labeled carriers. Claims 51 and 52 depend on Claim 50. The cited art does not teach or suggest such a method.

In view of the preceding amendments and remarks, it will be apparent that all claims in this case define a novel and non-obvious invention, and that the application is in condition for allowance and should be passed to issue without further delay. Should any further questions remain, the Examiner is asked to telephone applicant's attorney at the number listed below.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service in a sealed envelope as first class mail with postage thereon fully prepaid addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on February 4, 2004.

Kathy Powers

Date: February 4, 2004

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